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Therapeutic Review
Inhaled Antimuscarinics

Overview/Summary

The inhaled antimuscarinics (anticholinergics) are a class of bronchodilators primarily used in the management of chronic obstructive pulmonary disease (COPD). COPD is a condition characterized by progressive airflow restrictions that are not fully reversible.[1] Symptoms typically associated with COPD include dypsnea, cough, sputum production, wheezing and chest tightness. Specifically, inhaled antimuscarinics work via the inhibition of acetylcholine at parasympathetic sites in bronchial smooth muscle causing bronchodilation. Meaningful increases in lung function can be achieved with the use of inhaled antimuscarinics in patients with COPD.[1]

There are two inhaled antimuscarinics currently available, ipratropium (Atrovent® HFA) and tiotropium (Spiriva®). Both agents are Food and Drug Administration (FDA) approved for the maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. The two agents are distinguishable based on differences in pharmacokinetic parameters. Ipratropium, a short-acting bronchodilator, has a duration of action of six to eight hours requiring administration four times daily. The newer agent, tiotropium, has a duration of action of greater than 24 hours requiring once-daily administration and is classified as a long-acting bronchodilator. Comparative trials have reported that tiotropium may improve spirometry measurements to a greater degree than ipratropium.[2,3] Ipratropium is available as a meter dose aerosol inhaler for oral inhalation as well as a solution for nebulization.[4,5] Tiotropium is available as a dry powder inhaler for oral inhalation.[6] The ipratropium solution for nebulization is the only inhaled antimuscarinic product that is currently available generically.

In March of 2008, the manufacturers of Spiriva®, Boehringer Ingeheim Pharmaceuticals Inc., notified the FDA of results from a pooled analysis of 29 clinical trials that suggested a small excess risk of stroke (2 cases per 1,000) with tiotropium over placebo. Later, in October of 2008, the FDA released an updated statement informing healthcare professionals that preliminary results from a large, 4-year, placebo controlled clinical trial with Spiriva® in approximately 6,000 patients with COPD, demonstrated no increased risk of stroke with tiotropium compared to placebo.[7] During this same time, however, two studies were published reporting an increased risk for mortality and/or cardiovascular events in patients who received tiotropium or other inhaled antimuscarinics.[8,9] Results from one study demonstrated inhaled antimuscarinics significantly increased the risk of the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke, compared to patients receiving control therapy (P<0.001).[8]

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, inhaled therapy is preferred for the management of COPD and bronchodilators are central to symptom management.[1] The guidelines do not distinguish among the different classes of bronchodilators available (β_2-agonists, antimuscarinics and methylxanthines), and the choice of which agent to use depends on availability and patients' individual response in terms of symptom relief and side effects. In addition the GOLD guidelines state regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators. However, according to the National Institute for Clinical Excellence (NICE), long-acting bronchodilators should be used to control symptoms in patients who continue to experience problems despite the use of short-acting drugs.[10] NICE guidelines also state that a combination of bronchodilators from different pharmacologic classes may increase the efficacy of a COPD treatment regimen. Specifically for the management of acute COPD exacerbations, the addition of an inhaled antimuscarinics to a short-acting bronchodilator may be considered.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Ipratropium (Atrovent HFA®)	Inhaled antimuscarinic	✔ *
Tiotropium (Spiriva®)	Inhaled antimuscarinic	-

*Solution for nebulization.

Indications

Table 2. Food and Drug Administration Approved Indications[4-6]

Generic Name	Long-term, Once-daily, Maintenance Treatment of Bronchospasm Associated with Chronic Obstructive Pulmonary Disease, Including Chronic Bronchitis and Emphysema	Maintenance Treatment of Bronchospasm Associated with Chronic Obstructive Pulmonary Disease, Including Chronic Bronchitis and Emphysema
Ipratropium		✔
Tiotropium	✔	

According to the package insert, ipratropium nebulizer solution can be administered alone or with other bronchodilators, especially β_2-adrenergic agonists.[5]

In addition to its Food and Drug Administration (FDA) approved indication, ipratropium may also be used off-label as adjunctive therapy in moderate-to-severe exacerbations of acute asthma in patients presenting to an emergency department.

Pharmacokinetics

Table 3. Pharmacokinetics[1,11]

Generic Name	Onset (minutes)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Ipratropium	15	6-8	2.8	None	2.0-3.8
Tiotropium	60	24	74.0	None	120-144

Clinical Trials

The inhaled antimuscarinics have demonstrated good clinical efficacy and safety in improving lung function and exercise tolerance in patients with chronic obstructive pulmonary disease (COPD). A few head-to-head trials have noted significant differences in improvements in lung function favoring tiotropium over ipratropium.[2,3] There is inconsistent data regarding a clinical advantage of tiotropium over other long-acting bronchodilators.[13-15] However, when tiotropium is used in combination with a bronchodilator from a different pharmacologic class, a significant clinical advantage is demonstrated.[15,16] In comparison to other short-acting bronchodilators, ipratropium does not appear to offer any significant advantages.[17] But, as with tiotropium, improved outcomes are achieved when ipratropium is used in combination with other bronchodilators.[18,19]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Casaburi et al[20] Tiotropium 18 µg once a day vs placebo	DB, MC, PC, RCT Patients with COPD (at least 40 years of age) with a $FEV_1 \leq$ 60% of predicted normal and a FEV_1/FVC of $\leq$ 70% participating in 8 weeks of PR	N=108 25 weeks	Primary: Treadmill walking endurance time Secondary: TDI, SGRQ, rescue albuterol use	Primary: After 29 days of treatment, patients receiving tiotropium showed longer exercise endurance time than patients receiving placebo. The difference between the treatments was 1.65 minutes (*P*=0.183). Patients receiving tiotropium showed significantly longer exercise endurance times compared to placebo both after 13 weeks of treatment (including 8 weeks of PR) and following the termination of the PR program after 25 weeks of treatment. The mean differences were 5.35 minutes (*P*=0.025) and 6.60 minutes (*P*=0.018), respectively. The mean increase in endurance time from day 29 before PR to day 92 after PR was 80% in the tiotropium group and 57% in the placebo group (*P* value not reported). Secondary: On day 92, the mean TDI focal score for tiotropium was 1.75 and 0.91 for placebo. On day 176, the placebo group showed a decline in the TDI focal score to 0.08 while the improvement in the tiotropium group was maintained at 1.75. At 12 weeks following PR, the difference between treatment groups was 1.67 units (*P*=0.03; differences exceeding 1 unit were considered clinically meaningful). The SGRQ total score in the tiotropium group was lower (i.e., improved) on each test day compared to the placebo group. After PR, the SGRQ scores improved by 7.27 units in the tiotropium group compared with 3.41 units in the placebo group. The difference between the treatment groups was not statistically significant (*P* value not reported). On average, patients receiving tiotropium used approximately one dose less of albuterol rescue medication per day when compared to patients receiving placebo over 25 weeks of treatment (*P*<0.05).
Tashkin et al[21] Tiotropium 18 µg once a day	DB, PC, PG, RCT Patients ≥ 40	N=5,993 4 years	Primary: Yearly rate of decline in the mean FEV_1 pre-	Primary: The rate of decline in the mean post bronchodilator FEV_1 was greater in patients who prematurely discontinued a study drug as compared with those who completed the study period. There were no significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	years of age with moderate-to-very-severe COPD, with a FEV_1 of 70% or less after bronchodilation and a FEV_1/FVC of 70% or less		bronchodilator and post-bronchodilator from day 30 until end of DB treatment Secondary: Rate of decline in the mean FVC and SVC, SGRQ scores, COPD exacerbations and related hospitalizations, rate of death from any cause and from lower respiratory conditions	differences between the tiotropium group and the placebo group in the rate of decline in the mean value for FEV_1 either prebronchodilator (*P*=0.95) or post bronchodilator (*P*=0.21) from day 30 to the end of study-drug treatment. Secondary: There were no significant differences between the treatment groups in the rate of decline in the mean value for FVC either prebronchodilator (*P*=0.30) or post bronchodilator (*P*=0.84). The rate of decline in the mean value for SVC was not reported. Significant differences in favor of tiotropium were observed at all time points for the mean absolute change in the SGRQ total score (*P*<0.0001), although these differences on average were below what is considered to have clinical significance. The overall mean between-group difference in SGRQ total score at any time point was 2.7 (95% CI, 2.0 to 3.3) in favor of tiotropium (*P*<0.001). Tiotropium was associated with a significant delay in the time to first exacerbation, with a median of 16.7 months (95% CI, 14.9 to 17.9) in the tiotropium group and 12.5 months (95% CI, 11.5 to 13.8) in the placebo group. In addition, tiotropium was associated with a significant delay in the time to the first hospitalization for an exacerbation (*P* value not reported). The mean numbers of exacerbations leading to hospitalizations were infrequent and did not differ significantly between the two treatment groups (*P* value not reported). During the 4 year study, among patients for whom vital-status information was available, 921 patients died; 14.4% in the tiotropium group and 16.3% in the placebo group (HR, 0.87; 95% CI, 0.76 to 0.99). During the 4 year study period plus 30 days included in the intent-to-treat analysis, 941 patients died; 14.9% in the tiotropium group and 16.5% in the placebo group (HR, 0.89; 95% CI, 0.79 to 1.02).
Van Noord et al[2] Tiotropium 18 µg once a day	DB, DD, MC, PG Patients with	N=288 15 weeks	Primary: Changes in FEV_1 and FVC	Primary: The FEV_1 response, at all time points on days 8, 50, and 92, was significantly greater after tiotropium than after ipratropium (differences of

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vs ipratropium 40 µg four times a day	stable COPD with mean age of 65 years and average FEV_1 of 41% of predicted values		Secondary: Daily records of PEF, use of albuterol	0.09 L, 0.11 L, 0.08 L; *P*<0.05). The results for FVC closely reflect those obtained for FEV_1. Tiotropium performed consistently better than ipratropium. The differences in trough FEV_1 values were most pronounced (*P*<0.001), whereas differences in peak FEV_1 increase did not reach statistical significance (*P*>0.05). Secondary: The improvement in both morning and evening PEF was greater in the tiotropium group than in the ipratropium group. The difference in morning PEF between the groups was statistically significant up through week 10 (*P*<0.05). For evening PEF, the difference reached statistical significance during the first seven weeks of the treatment period (*P*<0.05). In both groups, there was a drop in the use of rescue albuterol, the reduction being greater in the tiotropium group than in the ipratropium group (*P*<0.05).
Vincken et al[3] Tiotropium 18 µg once a day vs ipratropium 40 µg four times a day	DB, DD, MC, PG, RCT Patients with COPD ≥40 years of age with an FEV_1 of ≤65% of predicted normal value and ≤70% of FVC	N=535 12 months	Primary: Changes in spirometry Secondary: PEFR, rescue albuterol use, BDI, TDI, SGRQ, QOL	Primary: By the end of day 8, the mean trough FEV_1 was 140 mL above baseline for patients in the tiotropium group (12% increase) compared with 20 mL for the ipratropium group. Tiotropium was more effective than ipratropium at all time points on all test days except for the first 2 hours following the first dose and up to 1 hour after the dose, 1 week later (*P*<0.05). At the end of one year, trough FEV_1 was 120 mL above the day 1 baseline for patients receiving tiotropium, and had declined by 30 mL for those receiving ipratropium (difference of 150 mL between groups; *P*<0.001 at all time points). The FVC results paralleled the FEV_1 results. At the end of one year, the trough FVC was 320 mL above the day 1 baseline for patients receiving tiotropium and 110 mL for those receiving ipratropium (mean difference of 210 mL between groups).

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				Secondary: Throughout the 1-year treatment period, morning and evening PEFR improved significantly more in the tiotropium group than in the ipratropium group (*P*<0.01 at all weekly intervals). On average, patients receiving tiotropium self-administered approximately 4 fewer inhalations of albuterol per week compared to patients receiving ipratropium (*P*<0.05 for 40 of the 52 weeks). The BDI focal scores for the two groups were comparable. Tiotropium significantly improved all components of the TDI on all test days compared to ipratropium (*P*<0.05). The proportion of patients who achieved a clinically meaningful difference in TDI focal score (improvement of ≥1 unit) at 1 year was significantly greater in the tiotropium group (31%) than in the ipratropium group (18%, *P*=0.004). During the 1-year treatment period, the SGRQ total score decreased (improved) in both groups, but gradually returned towards baseline in the ipratropium group. Improvements were maintained over the year in the tiotropium group, and were significantly better with ipratropium (difference of 3.30±1.13 on day 364, *P*<0.05). QOL, as assessed by the SF-36 questionnaire, suggested that tiotropium was more effective than ipratropium in all physical domains. The differences between treatment groups were only significant in physical health summary on the last 2 test days. In the mental health domains, the differences in scores between the two treatment groups were less consistent and generally not significant.
McCrory et al [17] Ipratropium (various strengths and dosage forms) vs	MA 9 RCT's of adult patients with a diagnosis of COPD, symptoms	N=525 Duration ranged from 1 hour to 14 days	Primary: Short-term changes in FEV_1, WMD of long-term effects on FEV_1	Primary: There was no significant difference in short-term FEV_1 changes (up to 90 minutes post dose) between individuals receiving ipratropium compared to a β_2-adrenergic agonist (*P* value not reported). The change in FEV_1 was not significant when ipratropium was added to a β_2-adrenergic agonist (WMD, 0.02 L; 95% CI, 0.08 to 0.12). These results

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β_2-adrenergic agonist (various strengths and dosage forms), a combination of β_2-adrenergic agonists and ipratropium (various strengths and dosage forms), or placebo	consistent with an acute exacerbation		Secondary: Not reported	were similar 24 hours post-dose (long-term) between the ipratropium and β_2-adrenergic agonist groups (WMD, 0.05 L; 95% CI, -0.14 to 0.05). Secondary: Not reported
Matera et al[18] Ipratropium 40 µg plus placebo vs salmeterol 50 µg plus placebo vs salmeterol 50 µg plus ipratropium 40 µg vs placebo plus placebo	RCT, SB, XO Male patients with COPD aged 40 years or older with an FEV_1 between 16% and 62% of predicted value	N=12 4 days	Primary: Changes in FEV_1 Secondary: Changes in the area under the FEV_1 response-time curve	Primary: The peak response (28.8%±5.0) for salmeterol was greater than that for ipratropium (26.0%±9.1), but equivalent peak bronchodilation occurred with salmeterol and salmeterol plus ipratropium (28.0±4.2). All active treatments produced a significant bronchodilation effect from 15 to 360 minutes, when compared with placebo (P<0.05), but only salmeterol and salmeterol plus ipratropium induced a significant (P<0.05) spirometric increase over the 12 hour monitoring period. Secondary: All of the AUC values for active treatments were significantly greater than for placebo (P<0.05), and that for salmeterol and salmeterol plus ipratropium were significantly (P<0.05) greater than that for ipratropium alone. There was no significant difference (P>0.05) between the salmeterol and salmeterol plus ipratropium AUC.
Van Noord et al[19] Salmeterol 50 µg plus ipratropium matched placebo vs salmeterol 50 µg plus ipratropium 40 µg	DB, MC, PG, RCT Patients with COPD aged 40-75 years with a FEV_1 ≤75% of predicted value	N=144 14 weeks	Primary: Spirometric changes after first dose of medication Secondary: Symptom scores, rescue medication used,	Primary: After inhalation of salmeterol, there was a mean + SEM peak increase in FEV_1 of 7.0%±0.7% predicted after 2 hours, followed by a plateau. After 12 hours, the improvement was still 2%±1% of predicted. Salmeterol plus ipratropium produced a peak increase in FEV_1 of 11.0%±0.8% predicted after 2 hours. After 12 hours, the improvement was 3.0%±0.8% predicted. The improvement in FVC in the two active treatment groups was similar to

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vs salmeterol-matched placebo plus ipratropium-matched placebo			PEF, clinic lung function, adverse events, exacerbations	that reported with FEV_1. Secondary: Throughout the treatment period there was a mean ± SEM decrease in the daytime symptom score from 1.9±0.1 to 1.7±0.1 in the placebo group (*P*=NS), from 2.0±0.1 to 1.4±0.1 (*P*<0.001) in the salmeterol group and from 2.0±0.1 to 1.3±0.1 (*P*<0.001) in the salmeterol plus ipratropium group. Compared with placebo, treatment with salmeterol and salmeterol plus ipratropium was associated with a higher percentage of days and nights without the use of additional albuterol (*P*<0.01). No difference was observed between the two active treatment groups (*P*=0.35). Improvements in morning PEF were significantly better in both active treatment groups than in the placebo group (*P*<0.001), whereas no difference was observed between the salmeterol and the salmeterol plus ipratropium groups. The changes in evening PEF were in favor of both active treatment arms compared with placebo (*P*<0.001), whereas the improvement was better in the salmeterol plus ipratropium group vs. the salmeterol group (*P*<0.01). During the 12-week treatment period, the mean ±SEM increase in FEV_1 was 1.0%±0.9% predicted for placebo, 5.0%±0.9% predicted for salmeterol, and 8.0%±0.8% for the salmeterol plus ipratropium group. All differences were statistically significant (*P*<0.01). The change in FVC was 4.0%±1.2% predicted after placebo, 7.0%±1.2% predicted after salmeterol, and 12.0%±1.2% after salmeterol plus ipratropium. The differences between salmeterol plus ipratropium vs. salmeterol alone and between salmeterol plus ipratropium vs. placebo were both significant (*P*<0.01), whereas there was no significant difference between the change in FVC after placebo and salmeterol (*P*=0.055). The reported incidence and nature of possible and probably drug-related side effects were similar among the three groups.

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				During the 12-week treatment period, 35 patients experienced a COPD exacerbation, 18 (36%) in the placebo group, 11 (23%) in the salmeterol group, and six (13%) in the salmeterol plus ipratropium group. The only significant difference was between the salmeterol plus ipratropium group and the placebo group (*P*<0.01).
Barr et al[12] Tiotropium vs placebo, or ipratropium, or a long-acting β_2-adrenergic agonists	MA 9 RCT's with patients diagnosed with COPD, whose disease was stable	N=6,584 1 month or greater	Primary: Exacerbations, hospitalizations, mortality Secondary: Change in FEV_1 and/or FVC, rescue medication use, adverse events	Primary: Reduced exacerbations seen in the tiotropium group compared to placebo (OR, 0.75; 95% CI, 0.66 to 0.85) and compared to ipratropium (OR, 0.64; 95% CI, 0.44 to 0.92). Hospitalizations for COPD exacerbations were reduced in the tiotropium group compared to placebo (OR, 0.65; 95% CI, 0.50 to 0.85) and compared to ipratropium and salmeterol but these differences were not statistically significant (OR, 0.59; 95% CI, 0.32 to 1.09; OR, 0.59; 95% CI, 0.29 to 1.23). Cumulative all-cause mortality was 1.5% in the control groups and there were no statistically significant differences between any of the treatment groups over the duration of the trials (*P* value not reported). Secondary: In the tiotropium group, there was a greater mean change in trough FEV_1 from baseline that was statistically significant compared to placebo (140 mL; 95% CI, 118 to 162 mL), ipratropium (150 mL; 95% CI, 106 to 193 mL) and salmeterol (40 mL; 95% CI, 12 to 68 mL). In the tiotropium group, there was a greater mean change in trough FVC from baseline that was statistically significant compared to placebo (278 mL; 95% CI, 208 to 348 mL) ipratropium (210 mL; 95% CI, 112 to 308 mL) and salmeterol (90 mL; 95% CI, 35 to 145 mL). In the tiotropium group, there was a greater mean change in morning peak flow from baseline that was statistically significant compared to the placebo (21 mL; 95% CI, 15 to 28 mL) and ipratropium (16 mL; 95% CI, 7 to 25 mL). There was no difference between the tiotropium and salmeterol groups (0 mL; 95% CI -8 to 9 mL).

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				In the tiotropium group, dry mouth was significantly increased compared to placebo (OR, 5.4; 95% CI, 3.3 to 8.8), ipratropium (OR, 2.1; 95% CI, 1.05 to 4.2), and salmeterol (OR, 5.1; 95% CI, 2.2 to 12.0).
Brusasco et al[13] Tiotropium 18 µg once a day vs salmeterol 50 µg twice a day vs placebo	DB, DD, PC, RCT Patients with COPD over the age of 40, with an FEV_1 ≤65% of predicted and an FVC ≤70%	N=1,207 6 months	Primary: Exacerbations, health resource use, restricted activity Secondary: SGRQ, TDI, spirometry, adverse events	Primary: Tiotropium significantly delayed the time to the first COPD exacerbation compared with placebo (*P*<0.01). The proportion of patients with at least one exacerbation was 32%, 35%, and 39% in the tiotropium, salmeterol, and placebo groups, respectively (*P*>0.05). The time to first hospital admission for a COPD exacerbation did not differ between any two treatment groups. The number of hospital admissions and days in hospital for any cause was lower in both the tiotropium and salmeterol groups than in the placebo group; however, the difference for salmeterol was not statistically significant (*P* value not reported). The lowest number of days on which patients were unable to perform their usual daily activities due to any cause was observed in the tiotropium group (8.3) compared with 11.1 days in the salmeterol group and 10.9 days in the placebo group (*P*<0.05). Secondary: The SGRQ total score improved by 4.2, 2.8, and 1.5 units during the 6 month trial for the tiotropium, salmeterol, and placebo groups, respectively. A significant difference was observed for tiotropium vs placebo (*P*<0.01). TDI focal scores improved in both the tiotropium (1.1 units) and salmeterol (0.7 units) groups compared with placebo (*P*<0.001 and *P*<0.05, respectively). There was no significant difference between the tiotropium and salmeterol groups (*P*=0.17). Tiotropium was statistically better than salmeterol in peak FEV_1 and AUC from 0 to 3 hours. For trough FEV_1 values, tiotropium exhibited a similar trend. Dryness of the mouth was the only event that was statistically higher with

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				tiotropium (8.2%) than with salmeterol (1.7%) or placebo (2.3%; *P* value not reported).
Donohue et al[14] Tiotropium 18 µg once a day vs salmeterol 50 µg twice a day vs placebo	DB, DB, MC, PC, PG, RCT Patients with stable COPD (age ≥40) with an FEV_1 ≤60% of predicted normal and FEV_1/FVC of ≤70%	N=623 6 months	Primary: Changes in spirometry Secondary: PEFR, TDI, SGRQ	Primary: At 24 weeks, trough FEV_1 had improved significantly over placebo by 137 mL in the tiotropium group and by 85 mL in the salmeterol group. The difference between tiotropium and salmeterol was significant (52 mL; *P*<0.01). As with FEV_1, the differences for FVC were significant for the active compounds over placebo, but tiotropium was significantly more efficacious than salmeterol for all variables. The difference between tiotropium and salmeterol was 112 mL and was statistically significant (*P*<0.01). Secondary: PEFR improved by 27.3 L/minute, 21.4 L/minute, and 0.3 L/minute for the tiotropium, salmeterol, and placebo groups, respectively, by the end of the study. Both active treatments were better than placebo (*P*<0.001) and tiotropium was better than salmeterol in improving evening PEFR (*P*<0.05). At 6 months, the improvement in TDI focal scores over placebo was 1.02 units for tiotropium (*P*=0.01), and 0.24 units for salmeterol (*P*=0.56). Tiotropium was better than salmeterol in improving TDI focal score (difference 0.78 units; *P*<0.05). At 6 months, the mean improvement in SGRQ was -5.14 units for tiotropium (*P*<0.05 vs placebo), -3.54 units for salmeterol (*P*=0.39 vs placebo), and -2.43 units for placebo. The difference between tiotropium and salmeterol did not reach statistical significance (*P* value not reported).
Aaron et al[15] Tiotropium 18 µg once a day plus placebo vs tiotropium 18 µg once a day	DB, MC, PC, PG, RCT Patients ≥35 years old with at least 1 COPD exacerbation in the last 12	N=449 1 year	Primary: Proportion of patients who experience a COPD exacerbation requiring systemic	Primary: The proportion of patients who experienced at least one COPD exacerbation in the tiotropium plus placebo group (62.8%) did not significantly differ between the tiotropium plus salmeterol group (64.8%) and the tiotropium plus fluticasone/salmeterol group (60.0%). The absolute risk reduction was -2.0 percentage points (95% CI, -12.8 to 8.8 percentage points) for the tiotropium plus salmeterol group versus

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plus salmeterol 50 µg twice a day vs tiotropium 18 µg once a day plus fluticasone/salmeterol 500/50 µg twice a day	months requiring systemic steroids or antibiotics, history of ≥10 pack-years of cigarette smoking, documented chronic airflow obstruction with an FEV_1/FVC <0.70 and a post-bronchodilator FEV_1 <65% of the predicted value		steroids or antibiotics Secondary: Mean number of COPD exacerbations per patient-year, total number of exacerbations resulting in urgent visits to a health care practitioner or emergency room, number of hospitalizations for COPD, total number of hospitalizations for all causes, changes in HRQL, dypsnea, and lung function	tiotropium plus placebo (*P*=0.71) and 2.8 percentage points (95% CI, -8.2 to 13.8 percentage points) for tiotropium plus fluticasone/salmeterol versus tiotropium plus placebo (*P*=0.62). The unadjusted odds ratio risk for exacerbations was 1.03 (95% CI, 0.63 to 1.67) with tiotropium plus salmeterol versus tiotropium plus placebo and 0.85 (95% CI, 0.52 to 1.38) for tiotropium plus fluticasone/salmeterol versus tiotropium plus placebo. Secondary: The mean number of COPD exacerbations per patient-year did not significantly differ between the tiotropium plus placebo group (1.61) and the tiotropium plus salmeterol group (1.75) and the tiotropium plus fluticasone/salmeterol group (1.37). The incidence rate ratio was 1.09 (95% CI, 0.84 to 1.40) for tiotropium plus salmeterol compared with tiotropium plus placebo (*P*=0.51) and 0.85 (95% CI, 0.65 to 1.11) for tiotropium plus fluticasone/salmeterol versus tiotropium versus tiotropium plus placebo (*P*=0.24). Patients treated with tiotropium plus fluticasone/salmeterol had lower rates of severe COPD exacerbations requiring hospitalization than did patients treated with tiotropium plus placebo with an incidence rate ratio of 0.53 (95% CI, 0.33 to 0.86; *P*=0.01). All-cause hospitalizations were reduced in patients treated with tiotropium plus placebo (*P*=0.04). Similar benefits were not seen for the tiotropium plus salmeterol compared with tiotropium plus placebo. The 1-year change in total score on the SGRQ was -4.5 points in the tiotropium plus placebo group, -6.3 points in the tiotropium plus salmeterol group (*P*=0.02), and -8.6 points in the tiotropium plus fluticasone/salmeterol group (*P*=0.01). Dypsnea scores improved over 1 year of observation but did not significantly differ among the treatment groups (*P*=0.38).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Over 52 weeks, the absolute prebronchodilator FEV_1 increased by 0.027 L in the tiotropium plus placebo group compared with 0.086 L in the tiotropium plus fluticasone/salmeterol group (*P*=0.049). Additionally, the percent predicted FEV_1 increased by 1.3% in the tiotropium plus placebo group compared with 4.6% in the tiotropium plus fluticasone/salmeterol group (*P*=0.005). Lung function was not significantly better in the tiotropium plus salmeterol group than in the tiotropium plus placebo group.
Rabe et al[16] Tiotropium 18 µg once a day plus formoterol 12 µg twice a day vs salmeterol 50 µg twice a day plus fluticasone 500 µg twice a day	DB, MC, PG, RCT Patients ≥40 years of age with a diagnosis of COPD, >10 pack-years smoking history, a post-bronchodilator FEV_1 <80% predicted and FEV_1/FVC < 0% at visit 1, and predose FEV_1 ≤65% predicted at visit 2	N=605 6 weeks	Primary: FEV_1 $AUC_{0-12,}$ peak FEV_1 Secondary: Morning predose FEV_1	Primary: After 6 weeks, the FEV_1 AUC_{0-12} mean difference was 78 mL higher (95% CI, 34 to 122 mL) with treatment with tiotropium plus formoterol compared to treatment with salmeterol plus fluticasone (*P*=0.0006). The difference in peak FEV_1 was 103 mL (95% CI, 55 to 150 mL) in favor of tiotropium plus formoterol (*P*<0.0001). Secondary: The difference in predose FVC after 6 weeks favored tiotropium plus formoterol (95% CI, 11 to 147 mL; *P*<0.05).
Singh et al[8] Any inhaled antimuscarinics for treatment of COPD	MA, SR 17 RCT's for any inhaled antimuscarinics with more than 30 days of follow up, study participants with a diagnosis of COPD of any	N=14,783 Duration ranged from 6 to 26 weeks	Primary: Composite of cardiovascular death, myocardial infarction, or stroke Secondary: All-cause mortality	Primary: In a MA of 17 trials of 14,783 participants, cardiovascular death, myocardial infarction, or stroke occurred in 1.8% (N=135) of patients receiving inhaled antimuscarinics and 1.2% (N=86) of patients receiving control therapy (RR, 1.58; 95% CI, 1.21 to 2.06; *P*<0.001). Among the individual components of the composite primary endpoint, inhaled antimuscarinics significantly increased the risk of myocardial infarction (1.2% vs 0.8% for control; RR, 1.53; 95% CI, 1.05 to 2.23; *P*=0.03) and cardiovascular death (0.9% vs 0.5% for control; RR, 1.80; 95% CI, 1.17 to 2.77; *P*=0.008) but did not significantly increase the risk of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	severity, an inhaled anticholinergic as the intervention drug vs a control, and reported data on the incidence of serious cardiovascular adverse events, including myocardial infarction, stroke, or cardiovascular death			stroke (0.5% vs 0.4% for control; RR, 1.46; 95% CI, 0.81 to 2.62; *P*=0.20). Secondary: Inhaled antimuscarinics did not significantly increased the risk of all-cause mortality (2.0% vs 1.6% for control; RR, 1.26; 95% CI, 0.99 to 1.61; *P*=0.06).
Lee et al[9] Exposure to inhaled corticosteroids, ipratropium, long-acting β_2-agonist, theophylline, and short-acting β_2-agonist	Nested case-control Patients treated in the United States Veterans Health Administration health care system	N=145,020 Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004	Primary: All-cause mortality, respiratory mortality, cardiovascular mortality Secondary: Subgroup analyses of primary outcomes	Primary: After adjusted for differences in covariates, inhaled corticosteroids and long-acting β_2-agonist were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for inhaled corticosteroids and 0.92 (95% CI, 0.88 to 0.96) for long-acting β_2-agonist was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15). Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared with the unexposed group (OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with long-acting β_2-agonist (OR, 1.12; 95% CI, 0.97 to 1.30), however the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with inhaled corticosteroids (OR, 0.88; 95% CI, 0.79 to 1.00), however this also did not reach statistical significance. Exposure to ipratropium was associated with a 34% increase in the odds of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas inhaled corticosteroids exposure was associated with a 20% decrease (OR, 0.80;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				95% CI, 0.72 to 0.88). Long-acting β_2-agonist (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR, 1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths. Secondary: In a sensitivity analysis based on dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication. With current smoking associated with a relative risk for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for inhaled corticosteroids, 1.08 for ipratropium, and 0.90 for long-acting β_2-agonist. Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of inhaled corticosteroids with ipratropium reduced the risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; $P<0.001$). In the all-cause mortality group, inhaled corticosteroids were consistently associated with reduced odds of death when used alone or in combination with other medications, whereas ipratropium and ipratropium plus theophylline were associated with elevated risk for death.

Study abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, SB=single-blind, SR=systematic review, XO=crossover

Study abbreviations: AUC=area under the curve, BDI=Baseline Dypsnea Index, CI=confidence interval, COPD=chronic obstructive pulmonary disease, CV=cardiovascular, ER=emergency room, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity, HR=hazard ratio, HRQL=health related quality of life, NS=not signficant, OR=odds ratio, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, PR=pulmonary rehabilitation, QOL=quality of life, RR=relative risk, SEM=standard error of the mean, SGRQ=St. George's respiratory questionnaire, SVC=slow vital capacity, TDI=transitional dypsnea index, WMD=weighted mean difference

Special Populations

Table 5. Special Populations[4-6]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Ipratropium	No dosage adjustment required in the elderly. Not studied in pediatric population.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown
Tiotropium	No dosage adjustment required in the elderly. Not studied in the pediatric population.	No dosage adjustment required.	Not studied in hepatic dysfunction.	C	Not studied in nursing mothers.

Adverse Drug Events

Due to poor absorption, systemic side effects associated with the use of inhaled antimuscarinics are limited. The most common side effect of these agents is dryness of the mouth, which is reported more with tiotropium.

Table 6. Adverse Drug Events [4-6]

Adverse Event(s)	Ipratropium	Tiotropium
Cardiovascular		
Arrhythmia	0.5	<1
Chest pain	-	2-7
Central Nervous System		
Depression	-	1-3
Dizziness	1-3	-
Headache	5-9	-
Paresthesia	-	1-3
Dermatological		
Allergic skin reactions	✔	2-4
Angioedema	✔	<1
Urticaria	✔	-
Endocrine and Metabolic		
Edema	-	3-5
Hypercholesterolemia	-	1-3
Hyperglycemia	-	1-3
Gastrointestinal		
Constipation	-	1-4
Dyspepsia	-	1-6
Gastrointestinal pain	-	3-6
Nausea	1-4	-
Vomiting	-	1-4
Genitourinary		
Urinary retention	✔	<1
Urinary tract infection	2-10	2-7
Musculoskeletal		
Arthralgia	-	3

Adverse Event(s)	Ipratropium	Tiotropium
Leg cramps	-	1-3
Myalgia	-	3-4
Respiratory		
Bronchitis	10-23	-
Bronchospasm	✔	-
Chronic obstructive pulmonary disease exacerbation	8-23	-
Coughing	3-6	3
Dypsnea	4-8	-
Pharyngitis	-	3-9
Rhinitis	2-6	2-6
Sinusitis	1-11	2-11
Upper respiratory tract infection	9-34	35-41
Other		
Accidents	-	5-13
Back pain	3-7	-
Dry mouth	2-4	3-16
Dysphonia	-	1-3
Epistaxis	-	1-4
Hypersensitivity reaction	✔	1-3
Infection	-	1-4
Influenza-like symptoms	2-8	3
Moniliasis	-	2-4
Mydriasis	✔	-

✔ Percent not specified.
- Event not reported.

Contraindications / Precautions[4-6]

Both ipratropium and tiotropium are contraindicated in patients with a history of hypersensitivity to atropine or its derivatives, or to any component of these agents.

Inhaled antimuscarinics are indicated for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD) and therefore should not be used as initial treatment of acute episodes of bronchospasm where rescue therapy is required for a rapid response.

Immediate hypersensitivity reactions may occur after the administration of inhaled antimuscarinics including anaphylaxis, angioedema, bronchospasm, oropharyngeal edema, rash, and urticaria. In addition, inhaled medicines may cause paradoxical bronchospasm.

Antimuscarinics should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction due to the potential to worsen signs and symptoms of these conditions. In addition, as a predominately renally excreted drug, patients with moderate to severe renal impairment should be monitored closely if treated with tiotropium.

In February 2008, the Food and Drug Administration (FDA) issued a public health advisory to highlight the correct use of Spiriva® (tiotropium) capsules. Spiriva® capsules are to be used in the specific Spiriva® HandiHaler® devices to deliver the medicine to the lungs. The capsules are specifically designed to be inhaled through inhalation devices and will not treat a patient's breathing condition if the contents of the capsule are swallowed rather than inhaled.[22]

Drug Interactions

Although the inhaled antimuscarinics are minimally absorbed, there is some potential for an additive interaction with concomitantly used antimuscarinic (anticholinergic) medications.

Table 7. Drug Interactions[11,23]

Generic Name	Interacting Medication or Disease	Potential Result
Inhaled antimuscarinics	Haloperidol	A decreased serum concentration of haloperidol and/or a development of tardive dyskinesia has been reported when anticholinergics were used with haloperidol.
Inhaled antimuscarinics	Phenothiazines	Anticholinergics may decrease the therapeutic effects of phenothiazines. This is probably due to the anticholinergic agent antagonizing the phenothiazine by direct central nervous system pathways. Acceleration of phenothiazine gut metabolism has also been postulated.
Inhaled antimuscarinics	Scopolamine	The anticholinergic activity of scopolamine may predispose the patient to excessive anticholinergic activity.

Dosage and Administration

Table 8. Dosing and Administration[4-6]

Generic Name	Adult Dose	Pediatric Dose	Availability
Ipratropium	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema: Aerosol for oral inhalation: initial, 34 µg (2 inhalations) four times daily; maximum, do not exceed 204 µg (12 inhalations) in 24 hours Solution for nebulization: maintenance, 500 µg four times daily, dose six to eight hours apart	Safety and efficacy in children have not been established.	Aerosol for oral inhalation: 17 µg (200 actuations per unit) Solution for nebulization: 500 µg (0.02%)
Tiotropium	Long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema: Powder for oral inhalation: initial, 18 µg once daily	Safety and efficacy in children have not been established.	Powder for oral inhalation: 18 µg

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
Global Initiative for Chronic Obstructive Lung Disease (GOLD): **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (COPD) (2008)[1]**	Diagnosis • A clinical diagnosis of COPD should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking. • A diagnosis of COPD should be confirmed by spirometry. • COPD patients typically display a decrease in both Forced Expiratory Volume in one second (FEV_1) and FEV_1/ Forced Vital Capacity (FVC) ratio. • The presence of a post-bronchodilator $FEV_1/FVC<0.70$ and $FEV_1<80\%$ predicted confirms the presence of airflow limitation that is not fully reversible. • A detailed medical history should be obtained for all patients suspected of developing COPD. • Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications.

Clinical Guideline	Recommendations
	• Bronchodilator reversibility testing should be performed to rule out the possibility of asthma. • Chest radiograph may be useful to rule out other diagnoses. • Arterial blood gas measurements should be performed in advanced COPD. • Screening for α_1-antitrypsin deficiency should be performed in patients of Caucasian decent who develop COPD at 45 years of age or younger. • Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis. <u>Treatment</u> • Patients should be instructed to avoid the exacerbating exposure. This includes assisting the patient in smoking cessation attempts and counseling the patient on how to avoid pollutant exposures. • The management of COPD should be individualized to address symptoms and improve the patient's quality of life. • None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and complications. • Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations. • Principle bronchodilators include β_2-agonists, anticholinergics and theophylline used as monotherapy or in combination. • The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. • For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators. • Inhaled corticosteroids should be used in patients with an FEV_1<50% of the predicted value. • Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. • COPD patients should receive an annual influenza vaccine. • The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV_1<40% of the predicted value. • Exercise training programs should be implemented for all COPD patients. • Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure. <u>Management of Exacerbations</u> • The most common causes of an exacerbation are bronchial tree infections and air pollution. • Inhaled β_2-agonists, with or without anticholinergics, and systemic corticosteroids are effective treatments for exacerbations of COPD. • Patients experiencing COPD exacerbations with clinical signs of airway infection may benefit from antibiotic treatment.

Clinical Guideline	Recommendations
National Institute for Clinical Excellence (NICE): **COPD: National Guideline on the Management of COPD in Adults in Primary and Secondary Care (2004)**[10]	Diagnosis • Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD. • The primary risk factor is smoking. • Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV_1<80% predicted and FEV_1/FVC<70%. Treatment • Smoking cessation should be encouraged for all patients with COPD. • Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation. • Long-acting bronchodilators ($beta_2$ agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators, if two or more exacerbations occur per year. • Inhaled corticosteroids should be added to patients on long-acting bronchodilators to decrease the frequency of exacerbations in patients with an $FEV_1 \leq 50\%$ of the predicted value. • Oral corticosteroids should be reserved for those patients with advanced COPD. • Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy. Plasma levels must be measured since there is a larger side effect burden with theophylline. • Pulmonary rehabilitation should be made available to patients. • Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure. Management of Exacerbations • Patients with exacerbations should be evaluated for hospital admission. • Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial. • Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days. • Oxygen should be given to maintain oxygen saturation above 90%. • Patients should receive invasive and noninvasive ventilation as necessary. • Respiratory physiotherapy may be used to help remove sputum. • Before discharge, patients should be evaluated by spirometry. • Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.

Conclusions

The inhaled antimuscarinics, ipratropium and tiotropium, are Food and Drug Administration (FDA) approved for the maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD).[4-6] Ipratropium and tiotropium are both classified as bronchodilators but due to differences in pharmacokinetic parameters, tiotropium is classified as a long-acting bronchodilator and ipratropium is classified as a short-acting bronchodilator. Tiotropium has a significantly longer duration of

action compared to ipratropium and as a result is approved for once-daily dosing. Ipratropium has a duration of action of six to eight hours and is administered four times daily. Both agents have been shown to improve lung function and exercise tolerance in patients with COPD however comparative trials have noted improved outcomes with tiotropium over ipratropium.[2,3] Improved outcomes are seen when either ipratropium or tiotropium are used in combination with other bronchodilators from different pharmacologic classes.

Current clinical guidelines do not distinguish among the different classes of bronchodilators used in the management of COPD.[1,10] However, the guidelines do state that long-acting bronchodilators should be used in patients who are not adequately controlled with short-acting bronchodilators.[10] In addition, the guidelines state that improved efficacy may be achieved when bronchodilators from different pharmacologic classes are used in combination for the management of COPD.

Recommendations

In recognition of the well-established role of inhaled antimuscarinics in the treatment of chronic obstructive pulmonary disease (COPD), no changes are recommended to the current approval criteria.

Single agent inhaled antimuscarinics (Atrovent HFA®, Spiriva®) are all preferred on the OVHA Preferred Drug List (PDL) and are available without a prior authorization.

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